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Office of Prevention, Pesticides
and
Toxic Substances

Note: This report combines the conclusions of the February, 1998 and October, 1999 HIARC meetings. No changes were made in hazard assessment or endpoint selection. This report supercedes TXR No(s). 012548 & 0013827.

TXR. NO. 0052152

MEMORANDUM

DATE: October 7, 2003

SUBJECT: **IPRODIONE: -Fourth** Report of the Hazard Identification Assessment Review Committee.

FROM: Linda L. Taylor, Ph.D. *Linda Lee Taylor*
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland, Chairman, *Jess Rowland*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Kelly O'Rourke, Risk Assessor
Registration Branch 3
Health Effects Division (7509C)

PC Code: 109801

The purpose of this report is to integrate the decisions of the February, 25, 1998 and the October, 26, 1999 Hazard Identification Assessment Review Committee meetings. At February 25, 1998 meeting, toxicology endpoints were selected for overall risk assessments (TXR No. 012548). At the October 26, 1999 meeting, a change was made to the toxicology endpoint selection for the intermediate term inhalation exposure risk assessment (TXR.No. 013827). The current report includes the conclusions of these two meetings.

RC
10/03

Committee Members in Attendance

Members present at the March 19, 1998 Meeting:

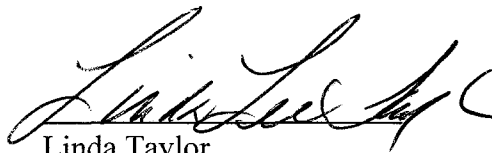
Karl Baetcke, William Burnam, Robert Fricke, Karen Hamernik, Susan Makris, Mike Metzger, Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Data were presented by Linda Taylor of Reregistration Branch 1.

Members present at the October 26, 199 Meeting:

William Burnam, Susan Makris, Nicole Paquette, Tina Levine, Pam Hurley, David Anderson, Mike Ioannou, PV Shah, Susan Makris, Nancy McCarroll, and Jess Rowland (Co-Chairman). Data were presented by Linda Taylor of Reregistration Branch 1.

Other HED members present at the meeting: Whang Phang.

Data Presentation:

A handwritten signature in black ink, appearing to read "Linda Taylor", written over a horizontal line.

Linda Taylor
Toxicologist

I. INTRODUCTION

On February 10, 1994 the Health Effects Division's RfD/Peer Review Committee established a Reference Dose (RfD) of 0.06 mg/kg/day based on a NOEL of 6.1 mg/kg/day established in a combined chronic toxicity/carcinogenicity study in rats and an Uncertainty Factor of 100 for inter-species extrapolation and intra-species variability (*Memorandum*: G. Ghali, HED to J. Housenger, SRRD, dated April 12, 1994).

On May 1, 1997, the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES Document dated May 1, 1997).

On October 16, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data to assess the potential enhanced sensitivity of infants and children from exposure to Iprodione as required by the Food Quality Protection Act (FQPA) of 1996 (TXR No. 012447).

On February 25, 1998, the HIARC met again to re-evaluate the toxicological endpoints for acute and chronic dietary as well as occupational and residential (dermal and inhalation) exposure risk assessments in light of a recently submitted prenatal developmental toxicity study in rats (MRID No. 44365001). The HIARC determined that the application of the FQPA safety factor for the protection of infants and children from exposure to Iprodione, as required by FQPA, will be determined during risk characterization (TXR No. 012548).

On October 26, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the toxicological endpoint for occupational (inhalation) exposure risk assessment in response to the Registrant's rebuttal of the occupational exposure assessment for the Iprodione Reregistration Eligibility Document (TXR No. 013827).

This report combines the conclusions of the February, 1998 and October, 1999 HIARC meetings. No changes were made in hazard assessment or endpoint selection. **This report supersedes TXR No(s). 012548 & 013827.**

II. HAZARD IDENTIFICATION

A. Acute Dietary : Females 13-50

Study Selected: Developmental Toxicity - Rat

§83-3a

MRID No. 44365001

Summary: In a special developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) received Iprodione (97.1%) in methylcellulose via gavage at dose levels of 0, 20, 120, or 250 mg/kg/day during gestation days 6 through 19. A positive control group received Flutamide at 50 mg/kg/day on the same treatment regimen. Maternal toxicity manifested as deaths in three dams at 250 mg/kg/day [days 18-20] and the early sacrifice of 6 additional dams of this group (days 15-20) due to the severity of clinical signs (prostration, reduced motor activity, and facial/urogenital staining). All dams in the other groups (except one vehicle control dam on day 11) survived until study termination. Clinical signs observed included staining of the skin/fur in the facial and anogenital area in three mid-dose dams (12%) and in all of the high-dose dams (100%), prostration in six high-dose dams, reduced/no motor activity in 10 high-dose dams, and staggering step in one high-dose dam. At 250 mg/kg/day, body weight was 90% of the control value on day 20 of gestation. Body-weight gains were significantly decreased at the 120 mg/kg/day (77% of control) and 250 mg/kg/day (59% of control) throughout the dosing period. Food consumption was decreased at 250 mg/kg/day from day 9, with the magnitude of the decrease increasing with time. There were no treatment-related gross pathology findings at the low-dose level, but there was a dose-related increase in enlarged adrenals at the mid- and high-dose levels at study termination. There were no abortions or premature deliveries, and no dams had 100% intrauterine deaths. All surviving dams had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, and live fetuses per dam among the groups. Only the high dose Iprodione group had dead fetuses (15 in one litter). There was no significant increase in pre- or postimplantation losses, but at 250 mg/kg/day, there was an increase in late resorptions compared to the control group and postimplantation loss was approximately double that of the control (13.5% vs 6.8%). The percent males was slightly greater at 250 mg/kg/day (56%) compared to the control (48%) and other dose groups (46%-48%), and fetal body weights were significantly decreased at 250 mg/kg/day (♂ 85%/♀ 86% of control) compared to the control. There was no treatment-related increase in the incidence of any external malformation [only malformation found was in a mid-dose Iprodione pup (cleft palate, partial)]. At 250 mg/kg/day, there was an increase in the number of runts and in the number of litters with runts compared to the vehicle and positive controls and the low- and mid-dose groups. Anogenital distance [AGD] in male pups was decreased significantly at 120 mg/kg/day (2.32 ± 0.12) and 250 mg/kg/day (2.10 ± 0.019) when compared to controls (2.43 ± 0.09); the incidence at 20 mg/kg/day was 2.44 ± 0.14 .

For maternal toxicity, the NOEL was 20 mg/kg/day, the LOEL was 120 mg/kg/day, based on decreased body-weight gain and decreased food efficiency. At 250 mg/kg/day, deaths occurred [9 out of 25] in addition to decreased body-weight gain and food consumption/efficiency. For developmental toxicity, the NOEL was 20 mg/kg/day and the LOEL was 120 mg/kg/day, based on decreased anogenital distance in the male pups. This perturbation in sexual development is independent of overall reductions in fetal growth.

Dose/Endpoint for establishing the Acute RfD: Developmental NOEL=20 mg/kg/day based on decreased anogenital distance (AGD) in male fetuses at 120 mg/kg/day (LOEL).

Comments about Study and Endpoint: The HIARC selected this dose (20 mg/kg/day) as a conservative estimate for risk assessment, however, doubted if this dose represented a "true" NOEL for the following reasons: 1) effects at the next higher dose (120 mg/kg/day, the LOEL), consisted of only marginal decreases; 2) although the decrease in AGD at the LOEL showed statistical significance, the biological significance is questionable because of the extent of the decreases seen between the NOEL (2.44 ± 0.14) and the LOEL (2.32 ± 0.12) which indicate that the "actual" no effect level could be higher, some where in between these levels (i.e., 20 and 120 mg/kg/day); 3) lack of evaluation of another critical endpoint (i.e., nipple development, characterized as areolas/nipple anlagen in two strains of rats) which was observed along with the decrease in AGD with Vinclozolin, a structurally related compound; and 4) although AGD was not measured, another developmental toxicity study in rats demonstrated a developmental NOEL of 90 mg/kg/day based on delayed fetal development (MRID 00162984).

The HIARC noted that the TES Committee selected the NOEL of 90 mg/kg/day established in the 1986 study along with an additional Uncertainty Factor of 3 due to the lack of data on the androgen deprivation effect. This yielded a dose ($90 \div 3 = 30$ mg/kg/day) which is comparable to the 20 mg/kg/day dose selected for this risk assessment.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability).

$$\text{Acute RfD} = \frac{20 \text{ mg/kg/day (NOEL)}}{100 \text{ (UF)}} = 0.2 \text{ mg/kg/day}$$

B. Chronic Dietary

(i). Reference Dose (RfD)

The HIARC concurred with the RfD established in 1994:

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat

§83-5

MRID Nos. 43308201 & 43000501

Executive Summary: In combined chronic toxicity/carcinogenicity study, groups of Sprague-Dawley rats were fed diets containing Iprodione at 0, 150, 300 or 1600 ppm for two years. These dose levels were equivalent to 0, 6.1, 12.4, and 69 mg/kg/day for males and 8.4, 16.5 and 95 mg/kg/day for females, respectively. The NOEL was 6.1 mg/kg/day for males and 8.4 mg/kg/day for females and the LOEL was 12.4 mg/kg/day for males and 16.5 mg/kg/day for females based on generalized enlargement of the cells of the zona glomerulosa and rarefaction and fine vacuolation of the zona fasciculata in the adrenal cortex in both sexes and histopathological changes in the male reproductive system.

Dose/Endpoint for establishing the RfD: NOEL=6.1 mg/kg/day based on histopathological lesions in the male reproductive system and effects on the adrenal glands in males at 12.4 and in females at 16.5 mg/kg/day (LOEL).

Comments about Study and Endpoint: The HIARC re-affirmed the dose and endpoints selected for establishing the RfD in 1994.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability).

$$\text{Chronic RfD} = \frac{6.1 \text{ mg/kg/day (NOEL)}}{100 \text{ (UF)}} = 0.06 \text{ mg/kg/day}$$

C. Occupational/Residential Exposure

1. Dermal Absorption

MRID No. 43535003

Dermal Absorption Factor: 5% at 10 hours.

Male Crl:CD BR rats were exposed dermally to Iprodione at dose levels of 0.4, 4.0, or 40 mg/rat (0.04, 0.4 or 0.4 mg/m²) for 0.5, 1, 2, 4, and 24 hours. Skin residue increased with the duration of exposure to 5-10% of the applied dose, although there was no apparent dose response. The portion of the test material absorbed increased with duration of exposure to .41%, 3.16%, and 0.19% of the applied dose at 0.4, 4.0 or 40 mg/rat, respectively. Absorption appears to be saturated at the two highest dose levels.

2. Short-Term Dermal - (1-7 days)

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: No dermal or systemic toxicity was seen following repeated dermal application of Iprodione at 0, 100, 500 or 1000 mg/kg/day, 6 hours/day, 5 days/week over a three week period to male and female New Zealand rabbits (MRID No. 42032301).

The HIARC concurred with the TES Committee's conclusions that there is no potential hazard via the dermal route because of the lack of systemic toxicity at the Limit-Dose (1000 mg/kg/day) and the demonstration of low (5%) absorption via the dermal route.

This risk assessment is **NOT** required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study and Endpoint: See Short-Term

This risk assessment is **NOT** required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat §83-5

MRID Nos. 43308201 & 43000501

Executive Summary: See Chronic Dietary

Dose/Endpoint for establishing the RfD: NOEL=6.1 mg/kg/day based on histopathological lesions in the male reproductive system and effects on the adrenal glands in males at 12.4 and in females at 16.5 mg/kg/day (LOEL).

Comments about Study and Endpoint: This dose was selected since the current use pattern (6 days/week for up to 180 days) indicates potential for Long-Term dermal exposures. This oral NOEL with a dermal absorption factor of 5% should be used only for non-cancer dermal risk assessments.

This risk assessment is required.

5. Inhalation Exposure

(i). Short-Term Exposure

Study Selected: Developmental Toxicity - Rat §83-3a

MRID No. 44365001

Executive Summary: See Acute Dietary

Dose/Endpoint for Risk Assessment: Developmental NOEL=20 mg/kg/day based on decreased AGD in male fetuses at 120 mg/kg/day (LOEL).

Comments about Study and Endpoint: The inhalation exposure component (i.e., µg a.i./lb/day) using a 100% absorption rate (default value) should be *converted to an equivalent oral dose* (mg/kg/day). This converted oral dose should then be compared to the NOEL identified above.

(ii). Intermediate-Term Exposure

Study Selected: Two Generation Reproduction - Rat §83-4

MRID No. 41871601

Executive Summary: In a two-generation reproduction study, male and female Sprague-Dawley received diets containing Iprodione (96.2%) at 0, 300, 1000, or 2000/3000 ppm (0, 18.5, 61.4, or 154.8 mg/kg/day for males and 22.49, 76.2, or 201.2 mg/kg/day for females) For parental systemic toxicity, the NOEL was 300 ppm (21 mg/kg/day) and the LOEL was 1000 ppm (69 mg/kg/day), based on decreased body weight, body weight gain, and food consumption in both sexes and

generations. For offspring toxicity, the NOEL was 1000 ppm (69 mg/kg/day) and the LOEL was 2000/3000 ppm (178 mg/kg/day), based on decreased pup viability (as evidenced by an increased number of stillborn pups and decreased survival during postnatal days 0-4), decreased pup body weight throughout lactation, and an increased incidence in clinical signs (smallness, reduced mobility, unkempt appearance, hunching, and/or tremors) in pups during the lactation period

Dose/Endpoint for Risk Assessment: Offspring NOEL=21 mg/kg/day based decrease body weight, body weight gain and food consumption at 69 mg/kg/day (LOEL).

Comments about Study and Endpoint: Previously, the HIARC selected the rat combined chronic toxicity/carcinogenicity study NOAEL [6.1 mg/kg/day] for the this risk assessment. The Registrant contends that the use of a chronic toxicity endpoint is inappropriate for assessing the risk resulting from intermediate-term exposures of seven days to several months. Comparing the subchronic and chronic oral rat studies, the data show that as the length of exposure increases, the effect and no-effect dose levels decrease; i.e., the endpoints of concern [histopathological lesions in the male reproductive system and in the adrenal of both sexes] were observed in the chronic study only at the high dose [69 mg/kg/day] at the interim sacrifice [12 months]. At the mid-dose level [12.4 mg/kg/day], these same lesions were observed only at the terminal sacrifice [2 years]. In the 90-day oral toxicity study, these same microscopic lesions were observed at 151 mg/kg/day and above, with a NOAEL of 78 mg/kg/day.

Although the Committee acknowledges that a shorter duration study, such as the subchronic study, would provide a more appropriate endpoint for use in an intermediate-term risk assessment, the selection of the subchronic study would result in the use of a value (69 mg/kg/day) that is greater than that used for short-term inhalation risk assessment (NOAEL of 20 mg/kg/day based on decreased anogenital distance in male offspring at 120 mg/kg/day). Therefore, the HIARC selected the 2-generation reproduction study NOAEL of 21 mg/kg/day for use in the intermediate-term inhalation risk assessment. The LOAEL is 69 mg/kg/day, based on decreased body weight, body-weight gain, and food consumption. Although the endpoint of concern is histopathological lesions in the male reproductive system and adrenal of both sexes observed in the 90-day and 2 year rat studies at 151 and 69 mg/kg/day, respectively, this selected NOAEL of 21 mg/kg/day would be protective of these effects. Additionally, the maternal NOAELs in the developmental toxicity studies in the rat and rabbit are 20 mg/kg/day.

(iii). Long-Term Exposure

The current use pattern does not indicate a concern for Long-Term exposure or risk. This risk assessment is **NOT** required.

D. Margin of Exposure for Occupational/Residential Exposures:

The appropriate MOEs will be determined during risk characterization.

E. Recommendation for Aggregate Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the oral NOEL to calculate the MOE.

For **short and intermediate** aggregate exposure risk assessment, combine the average exposure values from food + water together with the exposure from inhalation route (100% absorption) only and compare it to the oral NOELs to calculate the MOE (dermal risk assessments are not required for these exposure periods).

For **chronic** aggregate exposure risk assessment, combine the average exposure values from food + water together with the exposure from dermal route (5% dermal absorption) only and compare it to the oral NOEL to calculate the MOE (inhalation exposure risk assessment is not required for this exposure period).

IV. FQPA CONSIDERATIONS**1. Neurotoxicity Data**

There are no acute and subchronic neurotoxicity studies with Iprodione

2. Developmental Toxicity Data:

In a 1976 prenatal developmental toxicity study, groups of pregnant Sprague-Dawley rats (25-30/dose) received Iprodione (100%) in 1% carboxymethylcellulose via gavage at doses of 0, 100, 200, or 400 mg/kg/day during gestation days 5 through 15. For maternal toxicity, the NOEL was 200 mg/kg/day and the LOEL was 400 mg/kg/day based on slightly decreased body weight gain and significantly decreased food consumption. For developmental toxicity, the NOEL was 200 mg/kg/day and the LOEL was 400 mg/kg/day based on decreased implantation sites. This study does not appear to provide a robust evaluation of fetal effects following *in utero* exposure of Iprodione (MRID 0071324).

In a 1986 prenatal developmental toxicity study, groups of pregnant Sprague-Dawley rats were given oral (gavage) administrations of Iprodione (94.2%) in 0.5% methylcellulose at doses of 0, 40, 90, or 200 mg/kg/day during gestation days 6 through 15. No maternal toxicity was observed (maternal NOEL \geq 200 mg/kg/day). For developmental toxicity, the NOEL was 90 mg/kg/day and the LOEL was 200 mg/kg/day, based upon delayed fetal development, as evidenced by slightly reduced fetal weights and an increased incidence of space between the body wall and organs in fetuses (MRID 00162984).

In a 1997 special prenatal developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) received Iprodione (97.1%) in methylcellulose via gavage at dose levels of 0, 20, 120, or 250 mg/kg/day during gestation days 6 through 19. For maternal toxicity, the NOEL was 20 mg/kg/day, the LOEL was 120 mg/kg/day, based on decreased body-weight gain and decreased food efficiency. At 250 mg/kg/day, deaths occurred [9 out of 25] in addition to decreased body-weight gain and food consumption/ efficiency. For developmental toxicity, the NOEL was 20 mg/kg/day and the LOEL was 120 mg/kg/day, based on decreased anogenital distance in the male pups (MRID No. 44365001).

In a prenatal developmental toxicity study, pregnant New Zealand white rabbits (18/group), were given oral (gavage) administration of Iprodione (85%) in 0.5% Methocel at doses of 0, 20, 60, or 200 mg/kg/day during gestation days 6 through 18. For maternal toxicity, the NOEL was 20 mg/kg/day and the LOEL was 60 mg/kg/day based on decreased body weight gain. Also at 200 mg/kg/day, the following were observed: increased numbers of abortions, body weight loss, decreased food consumption and decreased defecation and urination. For developmental toxicity, the NOEL was 60 mg/kg/day and the LOEL was 200 mg/kg/day based upon increased skeletal variations (13th full rib, malaligned sternbrae, and 27 presacral vertebrae, occurring alone or in combination with each other or accompanied by delayed ossification) (MRID No. 00155469).

3. Reproductive Toxicity Data

In a two-generation reproduction study, male and female Sprague-Dawley received diets containing Iprodione (96.2%) at 0, 300, 1000, or 2000/3000 ppm (0, 18.5, 61.4, or 154.8 mg/kg/day for males and 22.49, 76.2, or 201.2 mg/kg/day for females) For parental systemic toxicity, the NOEL was 300 ppm (21 mg/kg/day) and the LOEL was 1000 ppm (69 mg/kg/day), based on decreased body weight, body weight gain, and food consumption in both sexes and generations. For offspring toxicity, the NOEL was 1000 ppm (69 mg/kg/day) and the LOEL was 2000/3000 ppm (178 mg/kg/day), based on decreased pup viability (as evidenced by an increased number of stillborn pups and decreased survival during postnatal days 0-4), decreased pup body weight throughout lactation, and an increased incidence in clinical signs (smallness, reduced mobility, unkempt appearance, hunching, and/or tremors) in pups during the lactation period. (MRID No. 41871601).

4. Determination of Susceptibility

The prenatal developmental toxicity study in rabbits, the special prenatal study in rats, and the two-generation reproduction study in rats demonstrated no indication of increased susceptibility to *in utero* and/or postnatal exposure to Iprodione.

In the 1986 prenatal developmental toxicity study in rats, however, developmental effects in the fetuses (a slight dose-related decrease in fetal weight and increased incidence of fetuses with a space between the body wall and the internal organs) were noted in the absence of

maternal toxicity. It is noted that the fetal findings were suggestive but not conclusive of fetal toxicity. Fetal weights were not altered in a statistically significant manner and were well within historical values. The incidence of space between the body wall and organs was also not apparently statistically significant. This finding may have been supportive (as were the c-section observations of "small fetus") of weight decrements in fetuses at the LOEL, but it could also be an artifact of preservative techniques. Also, the fetal findings were marginal and not statistically significant, within ranges of historical control values, and were not supported by data from other studies. Therefore, due to the lack of confidence in these data, the findings of this study were not judged to be an appropriate measure of potential sensitivity following *in utero* exposure to Iprodione.

Based on the weight-of-the-evidence of all available studies, the Committee concluded that there was no increased susceptibility to rat and rabbit fetuses following *in utero* and/or post natal exposure to Iprodione.

5. Recommendation for a Developmental Neurotoxicity Study

Based on the following weight-of-the-evidence considerations, the HIARC determined that a developmental neurotoxicity study in rats is **not** required for Iprodione.

(i) Evidence that support requiring a developmental neurotoxicity study:

- Overall, Iprodione does not appear to be a frankly neurotoxic chemical. There were no effects on brain weight or histopathology (nonperfused) of the nervous system in the chronic studies in rats, mice, and dogs. Findings that were suggestive of neurotoxicity (see below) were often equivocal, unsupported by data from other studies, and/or observed only at doses which compromised the survival of the animals.
- No evidence of developmental anomalies of the fetal nervous system was observed in the prenatal developmental toxicity studies in either rats or rabbits, at developmentally and/or maternally toxic oral doses up to 200 mg/kg/day.
- Evaluation of the special postnatal developmental toxicity study did not reveal any endpoints of concern that would trigger a developmental neurotoxicity study.

(ii) Evidence that would suggest the need for a developmental neurotoxicity study:

- In the chronic toxicity study in rats, degeneration of the sciatic nerve was observed after 2 years of dietary exposure to Iprodione. This finding was also observed at a relatively high incidence in control animals, although the

incidence doubled for females at the highest dose tested (1600 ppm).

- In the carcinogenicity study in mice, absolute brain weight was slightly decreased and adjusted brain weight was significantly decreased at the HDT (4000 ppm).
- In the 90-day subchronic study in rats, absolute brain weight was significantly decreased for females only at the HDT (3000 ppm). Clinical signs of toxicity in this study included piloerection and hunched posture at 3000 and 5000 ppm (the 5000 ppm treatment group was terminated early due to severe toxicity).
- In the two-generation reproduction study in rats, clinical observations in pups included reduced mobility, unkempt appearance, hunching, and/or tremors at the HDT (2000/3000 ppm = 178 mg/kg/day). At this treatment level, severe toxicity was observed in the parental animals, pup body weight was reduced, and pup survival was compromised.
- Iprodione causes endocrine disruption, affecting the reproductive system, pituitary, adrenals, and/or thyroid in various studies.

(iii) Other Unknown Factors:

- Because of the lack of acute and subchronic neurotoxicity studies in rats, there was no evaluation of the nervous system following perfusion. Findings in other studies that were suggestive of neurotoxicity could not be confirmed or refuted.

6. Determination of the FQPA Factor:

The application of an FQPA factor to ensure the protection of infants and children from exposure to Iprodione, as required by FQPA, will be determined by the FQPA Safety Factor Assessment Review Committee.

VI. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158. In 1994, the RfD Committee recommended a postnatal developmental toxicity study in rats due to the close structural similarity of Iprodione to Vinclozolin and because of the effects seen in the reproductive system of male rats as well as in the adrenal glands of both sexes of rats in the combined chronic toxicity/carcinogenicity study. In response to the above recommendation, the Registrant in 1997 submitted a special study that examined the sex differentiation of offspring from pregnant rats exposed orally to Iprodione (MRID No. 44365001).

The HIARC determined that there are outstanding questions with regard to postnatal exposure that remain to be addressed in light of the observed effects of Iprodione on the testes and its proposed mode of action (disruption of testosterone biosynthesis). Iprodione has been shown to alter anogenital distances in male fetuses following exposure during late gestation and there is evidence of toxicity to the male reproductive organs in chronic studies in rats. Also, no data are available on the effect of Iprodione on sperm count, motility or morphology in rat or other species. Therefore, the HIARC concluded that an assessment of effects on the male reproductive system following pre and/or postnatal exposure is required and these aspects can be addressed by conducting the study as described in OPPTS 870.3800

VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	Developmental NOEL=20	Decreased anogential distance in male pups.	Developmental- Rat
	UF=100	Acute RfD = 0.2 mg/kg/day	
Chronic Dietary	NOEL=6.1	Histopathological lesions in the male reproductive system and the adrenal glands in both sexes.	Combined Chronic Toxicity/ Carcinogenicity -Rat
	UF=100	Chronic RfD = 0.06 mg/kg/day	
Short-Term (Dermal)	Not Applicable	No dermal or systemic toxicity seen at the Limit-Dose in a 21-day dermal toxicity study in rabbits. This risk assessment is not required.	
Intermediate-Term (Dermal)	Not Applicable	No dermal or systemic toxicity seen at the Limit-Dose in a 21-day dermal toxicity study in rabbits. This risk assessment is not required.	
Long-Term (Dermal) ^a	Oral NOEL=6.1	Histopathological lesions in the male reproductive system and the adrenal glands in both sexes.	Combined Chronic Toxicity/ Carcinogenicity-Rat
Short-Term (Inhalation) ^a	Developmental NOEL=20	Decreased anogential distance in male pups.	Developmental-Rat
Intermediate-Term (Inhalation) ^a	Oral NOEL=21	Decreased body weight, body-weight gain, food consumption	2-generation reproduction-Rat
Long-Term (Inhalation)	Not Applicable	Based on the use pattern, there is no concern for exposure or risk. This risk assessment is not required.	

a = Appropriate route-to-route extrapolation should be performed (i.e., a dermal absorption factor of 5% and an inhalation absorption factor of 100% used for conversion to oral equivalent doses and then compared to the oral NOELs).



13544

R086424

Chemical: Iprodione

PC Code: 109801

HED File Code 21100 HIARC Reports

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